RESPONSE

To Ms. Shoko Yamamura, Examiner of the Patent Office

1. Indication of International Application

PCT/JP2004/008471

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4. Date of Notice 24.08.2004

5. Contents of response

(1) In the Written Opinion dated August 24, 2004 (mailing date), the Examiner cites the following Reference 1 (CHEST Vol. 123, No. 5 (May 2003) p. 1375-1375) and holds as follows:

"Claims 1, 8, 9, 12, 16 and 24:

Reference 1 describes measurement of the D-dimer level in patients suspected to have acute aortic dissection, and describes that, as a result of the aforementioned measurement, all acute aortic dissection patients turned positive in a D-dimer test, the measurement of D-dimer is expected to be an essential element for the initial evaluation of patients suspected to have aortic dissection, and, as a measurement method of D-dimer, a latex wherein a specific monoclonal antibody is bound with D-dimer is used for the measurement.

The invention relating to claims 1, 8, 9, 12, 16 and 24 is described in Reference 1 and lacks novelty."

In view of the viewpoints of the Examiner regarding the invention relating to claims 1, 8, 9, 12, 16 and 24, we have amended claims 1, 12 and 24 as shown in the Amendment submitted on the same date. We would respectfully submit our opinion regarding the novelty and inventive step of the invention relating to claims 1, 8, 9, 12, 16 and 24, in the following.

(2) Gist and characteristics of the invention relating to claims 1, 8, 9, 12, 16 and 24

(i) Gist of the invention relating to claims 1, 8, 9, 12, 16 and 24

Claims 1, 8, 9, 12, 16 and 24 as described in the Amendment submitted on the same date are as follows:

"1. A method of evaluating acute aortic dissection, which comprises measuring a D-dimer concentration in blood separated from a human, and determining that acute aortic dissection has been possibly developed if the measured concentration is not lower than a D-dimer cutoff value in blood which is pre-established between acute aortic dissection and acute myocardial infarction.

8. The evaluation method for acute aortic dissection of any of claims 1 to 4, wherein the measurement of D-dimer concentration in blood is performed by an immunochemical method.

9. The evaluation method of claim 8, wherein the immunochemical method is an enzyme immunochemical method, a latex aggregation method, or an immunochromatography method.

12. A reagent for evaluating the onset of acute aortic dissection, which comprises an antibody that recognizes a D-dimer, wherein a cutoff value is pre-established between acute aortic dissection and acute myocardial infarction.

16. The reagent of any of claims 12 to 15, wherein the antibody is a monoclonal antibody.

24. Use of an antibody that recognizes a D-dimer, for producing the reagent for evaluating the onset of acute aortic dissection of claim 12."

In claim 1, "determining whether or not acute aortic dissection has developed, on the basis of the measured concentration" has been amended to "determining that acute aortic dissection has been possibly developed if the measured concentration is not lower than a D-dimer cutoff value in blood which is pre-established between acute aortic dissection

and acute myocardial infarction".

In claims 12 and 24, a "reagent for evaluating" has been amended to a "reagent for evaluating the onset of". In claim 12, "wherein a cutoff value is pre-established between acute aortic dissection and acute myocardial infarction" has been added and in claim 24, "described in claim 12" has been added.

These amendments are within the scope of the items described in the original specification and the like, and do not add a new matter.

The amendments to claims 13 and 14 are formal ones resulting from the amendments to claim 12.

(ii) Characteristics of the invention relating to claims 1, 8, 9, 12, 16 and 24

The invention relating to claims 1, 8, 9, 12, 16 and 24 relates to a method of evaluating the onset of acute aortic dissection, a reagent useful for the evaluation method and use of a D-dimer antibody for the production of the reagent.

Conventionally, it had been known that the D-dimer concentrations in blood from patients with acute aortic dissection or acute myocardial infarction tend to be higher than those in healthy people.

On the other hand, the inventors of this application measured the D-dimer concentrations in blood from patients developing acute aortic dissection, and found that much higher concentrations of D-dimer are present in patients with acute aortic dissection than in patients with acute myocardial infarction, who are known to have higher concentrations of D-dimer in their blood than healthy people (lines 20-27, page 3 of this specification), thus developed the present invention relating to a method of determining acute aortic dissection based on measurements of D-dimer concentration in bloods and the like. The invention of this application is useful because it makes it possible to lower the false positive rate of acute myocardial infarction, and to evaluate acute aortic dissection.

(3) Particulars of prior art

Reference 1: CHEST Vol. 123, No. 5 (MAY 2003), pp. 1375-1378

① Cutoff value

Reference 1 states that the cutoff value of 0.5 μg/mL used was established to exclude deep vein thrombosis (DVT) (see lines 5-7, left column, page 1376).

② Evaluation of the non-onset of acute aortic dissection

Reference 1 states, "These data provide evidence that a

negative d-dimer test result could be useful in excluding acute thoracic aortic dissection" (see CONCLUSION, right column, page 1378). Therefore, it is stated that it is possible to evaluate the non-onset of acute aortic dissection on the basis of the result of a measurement of D-dimer concentration in blood.

③ Evaluation of the onset of acute aortic dissection

Reference 1 states that as affirmed by the examiner, all patients with acute aortic dissection tested positive in D-dimer test (lines 2-3 from bottom, left column, page 1376). On the other hand, it states, "the low specificity makes the interpretation of a positive value difficult" (lines 2-3 from bottom, left column, page 1378). Therefore, Reference 1 cannot be said to state that it is possible to evaluate the onset of acute aortic dissection on the basis of the results of a measurement of D-dimer concentration in blood.

(4) Comparison of the inventions relating to claims 1, 8, 9, 12, 16, and 24 and the cited inventions

① Comparison of the inventions relating to claims 1, 8, and 9 and Reference 1

There is a difference in that the method of claim 1 employs a cutoff value pre-established between acute aortic dissection and acute myocardial infarction, whereas the method of Reference 1 employs a cutoff value established by DVT. There is another difference in that the method of claim 1 is intended to evaluate the onset of acute aortic dissection, whereas the method of Reference 1 is intended to evaluate the non-onset of acute aortic dissection. Consequently, claims 1, 8, and 9 are not the invention described in Reference 1.

Additionally, claims 1, 8, and 9 are not obvious to those skilled in the art from Reference 1. This is because there is no suggestion about the cutoff value described in claim 1 in Reference 1, and also because Reference 1 makes it possible to evaluate the non-onset of acute aortic dissection. Furthermore, the inventions relating to claims 1, 8, and 9 have the advantageous effect of being capable of evaluating acute aortic dissection, while lowering the false positive rate of acute myocardial infarction.

Hence, we are confident that the inventions relating to claims 1, 8, and 9 have novelty and inventive step.

② Comparison of the inventions relating to claims 12, 16, and 24 and Reference 1

Amended claims 12, 16, and 24 relate to reagents for evaluating the onset of acute aortic dissection and use of a D-dimer antibody for producing the reagents, respectively. We have eliminated the reagents for evaluating the non-onset of acute aortic dissection and the use of a D-dimer antibody for producing the reagents from claims 12 and 24 before the amendment, respectively. Furthermore, we have limited the coverage to reagents for which a cutoff value is established between acute aortic dissection and acute myocardial infarction. Consequently, claims 12, 16, and 24 are not the invention described in Reference 1.

In addition, claims 12, 16 and 24 are not obvious to those of ordinary skill in the art from Reference 1 for the same reason as set forth in the above (4)(i).

From the foregoing, we believe that the invention relating to claims 12, 16 and 24 has novelty and an inventive step.

(5) Conclusion

As described in detail in the above, we believe that the Examiner will fully appreciate that the invention relating to claims 1, 8, 9, 12, 16 and 24 has novelty and an inventive step over Reference 1.

**AMENDMENT**

(Amendment according to provision of Article 11)

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4. Object of amendment Claims

5. Contents of amendment

As shown in the attached sheets.

[Items amended]

(1) In claim 1, "determining whether or not acute aortic dissection has developed, on the basis of the measured concentration" has been amended to "determining that acute aortic dissection has been possibly developed if the measured concentration is not lower than a D-dimer cutoff value in blood

which is pre-established between acute aortic dissection and acute myocardial infarction".

(2) In claim 12, "a reagent for evaluating ····" has been amended to "a reagent for evaluating the onset of ····, wherein a cutoff value is pre-established between acute aortic dissection and acute myocardial infarction".

(3) Claim 13 has been amended to "a reagent for evaluating Stanford type A acute aortic dissection, which comprises an antibody that recognizes a D-dimer."

(4) Claim 14 has been amended to "A reagent for evaluating Stanford type B acute aortic dissection, which comprises an antibody that recognizes a D-dimer."

(5) In claim 24, "a reagent for evaluating acute aortic dissection" has been amended to "the reagent for evaluating the onset of acute aortic dissection of claim 12".

6. List of the annexed document

New substitute sheets of claims,
pages 36-40 One copy

## Amended Claims under Art.34

1. (amended) A method of evaluating acute aortic dissection, which comprises measuring a D-dimer concentration in blood separated from a human, and determining that acute aortic dissection has been possibly developed if the measured concentration is not lower than a D-dimer cutoff value in blood which is pre-established between acute aortic dissection and acute myocardial infarction.

2. A method of evaluating acute aortic dissection, which comprises measuring a D-dimer concentration in blood separated from a human, and determining whether or not Stanford type A acute aortic dissection has developed, on the basis of the measured concentration.

3. A method of evaluating acute aortic dissection, which comprises measuring a D-dimer concentration in blood separated from a human, and determining whether or not Stanford type B acute aortic dissection has developed, on the basis of the measured concentration.

4. A method of evaluating acute aortic dissection, which comprises measuring a D-dimer concentration in blood separated from a human developing acute aortic dissection, and determining whether the developed acute aortic dissection is Stanford type A acute aortic dissection or Stanford type B acute aortic dissection, on the basis of the measured concentration.

5. A method of distinguishing between acute aortic dissection and acute myocardial infarction, which comprises measuring a D-dimer concentration in blood

separated from a human having an episode of chest pain, and determining which disease has developed whether acute aortic dissection or acute myocardial infarction, on the basis of the measured concentration.

6. The distinguishing method of claim 5, which comprises comparing the measured D-dimer concentration in blood and a D-dimer cutoff value in blood which is pre-established between acute aortic dissection and acute myocardial infarction, and determining that acute aortic dissection has developed if said concentration is not lower than said cutoff value, and acute myocardial infarction has developed if said concentration is lower than said cutoff value.

7. A method of distinguishing between acute aortic dissection and acute myocardial infarction, which comprises measuring a D-dimer concentration in blood separated from a human having an episode of chest pain, and determining which disease has developed whether Stanford type A acute aortic dissection, Stanford type B acute aortic dissection, or acute myocardial infarction, on the basis of the measured concentration.

8. The evaluation method for acute aortic dissection of any of claims 1 to 4, wherein the measurement of D-dimer concentration in blood is performed by an immunochemical method.

9. The evaluation method of claim 8, wherein the immunochemical method is an enzyme immunochemical method, a latex aggregation method, or an immunochromatography method.

10. The method of distinguishing between acute aortic dissection and acute myocardial infarction of any of claims 5 to 7, wherein the measurement of D-dimer concentration in blood is performed by an immunochemical method.

11. The distinguishing method of claim 10, wherein the immunochemical method is an enzyme immunochemical method, a latex aggregation method, or an immunochromatography method.

12. (amended) A reagent for evaluating the onset of acute aortic dissection, which comprises an antibody that recognizes a D-dimer, wherein a cutoff value is pre-established between acute aortic dissection and acute myocardial infarction.

13. (amended) A reagent for evaluating Stanford type A acute aortic dissection, which comprises an antibody that recognizes a D-dimer.

14. (amended) A reagent for evaluating Stanford type B acute aortic dissection, which comprises an antibody that recognizes a D-dimer.

15. A reagent for distinguishing between Stanford type A acute aortic dissection and Stanford type B acute aortic dissection, which comprises an antibody that recognizes a D-dimer.

16. The reagent of any of claims 12 to 15, wherein the antibody is a monoclonal antibody.

17. A reagent for distinguishing between acute aortic

dissection and acute myocardial infarction, which comprises an antibody that recognizes a D-dimer.

18. The distinguishing reagent of claim 17, which is a reagent for distinguishing between Stanford type A acute aortic dissection and acute myocardial infarction.

19. The distinguishing reagent of claim 17, which is a reagent for distinguishing between Stanford type B acute aortic dissection and acute myocardial infarction.

20. The distinguishing reagent of claim 17, which is a reagent for distinguishing among Stanford type A acute aortic dissection, Stanford type B acute aortic dissection, and acute myocardial infarction.

21. The distinguishing reagent of any of claims 17 to 20, wherein the antibody is a monoclonal antibody.

22. A commercial package comprising the reagent of any of claims 12 to 15 and a printed matter on the reagent, wherein the printed matter and/or the package bears the statement that the reagent can be used, or should be used, for the purpose of evaluating acute aortic dissection.

23. A commercial package comprising the distinguishing reagent of any of claims 17 to 20 and a printed matter on the reagent, wherein the printed matter and/or the package bears the statement that the reagent can be used, or should be used, for the purpose of distinguishing between acute aortic dissection and acute myocardial infarction.

24. (amended) Use of an antibody that recognizes a D-dimer, for producing the reagent for evaluating the onset of acute aortic dissection of claim 12.

25. Use of an antibody that recognizes a D-dimer, for producing a reagent for distinguishing between acute aortic dissection and acute myocardial infarction.